

EDITORIAL COMMENT

Mitral Valve Abnormalities in Congestive Heart Failure

An Interplay Between Form and Function?*

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Mitral regurgitation (MR) of at least mild severity is present in up to 90% of patients with advanced congestive heart failure (CHF) due to systolic dysfunction (1). It had long been assumed that MR results primarily from left ventricular (LV) and mitral annular enlargement due to pathologic remodeling, with contributions as well from regional wall motion abnormalities and papillary muscle dysfunction in patients with ischemic cardiomyopathy. It was recognized several years ago that, although diuretic and vasodilator therapy in CHF had little effect on LV ejection fraction, one of its major beneficial effects was a reduction in MR volume over the short (2) and intermediate (3) terms. Other

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approaches to reduction of MR in CHF, such as mitral valve reconstruction (4) or percutaneous mitral valve annuloplasty (5), are continuing to evolve, and their clinical benefits are less certain (6). Another, more recently appreciated contributor to MR in patients with CHF is dyssynchronous ventricular contraction, which is present in up to 50% of patients with CHF and depressed LV function (7). Reduction in MR may account for at least some of the clinical benefits seen in recent trials of biventricular pacing (8,9), although it represents but one of several measurable hemodynamic improvements seen with this therapy (10).

Abnormal mitral valve composition in CHF. However, it generally also has been assumed that although cardiac chamber sizes and mitral annular diameter increase in patients with CHF, the structure and composition of the mitral valve leaflets remain normal. This assumption is challenged by important findings of Grande-Allen et al. (11), who report in this issue of the *Journal* that mitral valve leaflets of patients with end-stage CHF have significant alterations in both cellularity and extracellular matrix (ECM) composition. Grande-Allen et al. (11) compared control valves, obtained at autopsy from gender- and age-matched patients, with mitral valves explanted at the time of

cardiac transplantation from patients with end-stage CHF. They found that, as compared with control valves, mitral leaflets of the CHF patients had 78% greater deoxyribonucleic acid content, indicating increased cellularity, as well as significant changes in ECM composition, including an 11% increase in collagen content and a 59% increase in glycosaminoglycans (GAGs) (11).

Cardiac structural abnormalities and alterations in valve composition: cause and effect or consequences of a common cause? The explanation for the changes in leaflet composition is perhaps more debatable. The authors' primary hypothesis was that changes in cardiac and valvular dimensions and function, as measured by echocardiography, would correlate with valvular composition changes. The implicit assumption here is that, as suggested by previous studies of surgically induced MR (12,13), direct hemodynamic forces are the major driver of valvular compositional change; neurohormones were not examined in those studies. However, the echocardiography/valvular composition correlations were arguably less striking. In fact, in multivariate modeling, the degree of MR was not correlated with any of the observed valvular compositional changes. Instead, most echocardiographic parameters found to correlate with leaflet changes were those that are themselves a consequence of tissue remodeling, such as left atrial, LV, and mitral annular size. This raises the possibility that, instead of direct hemodynamic forces representing the primary cause that effects changes in valvular composition, changes in cardiac chamber size and changes in valvular composition result from a common cause, such as the neurohormonal activation that accompanies CHF (14). Within valves there are regional differences in cell type, cell phenotype, and ECM composition, all of which have profound effects on cellular responses (15). Thus, it is not likely that different valve regions would respond similarly to neurohormones.

The effect of neurohormonal activation on myocardial fibrosis may occur primarily through effects on cardiac myocytes, in which beta-adrenergic receptor overactivity increases apoptosis (16) and beta-adrenergic blockade alters the expression of myosin isoforms and calcium-handling proteins (17). The stimulation of alpha-1-adrenergic receptors has recently been shown to increase production of connective tissue growth factor (18), a growth factor that has been implicated in many fibrosing diseases and which may be a downstream effector for the profibrotic growth factor, transforming growth factor (TGF)-beta-1 (19). However, effects of catecholamines on cardiomyocytes are unlikely to have any local effect on valve fibroblasts.

More direct effects on cardiac fibroblasts have been shown with activation of the renin-angiotensin aldosterone system. For example, aldosterone stimulates production of collagen types I and III by cardiac fibroblasts in vitro (20), and aldosterone antagonists have been shown to improve survival in CHF patients (21,22). Angiotensin II (AngII) also has been shown to stimulate collagen production by

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cardiac fibroblasts (20), an effect that may be due, in part, to production of TGF-beta-1 in response to angiotensin II type 1 receptor (AT1R) stimulation (23). In addition, tumor necrosis factor-alpha, circulating levels of which are markedly increased in CHF (24), upregulates cardiac fibroblast AT1R expression (25). Thus, not only are AngII levels increased in CHF patients, but their cardiac fibroblasts likely also express increased AT1R.

However, the most striking ECM change in the CHF valves of the Grande-Allen et al. (11) study was a 59% increase in GAGs. Glycosaminoglycans are molecules composed of repeating polysaccharides that can be found either covalently bound to a core protein to form proteoglycans (PGs) or without a core protein, as in the molecule hyaluronan. During the early phases of fibrosing injuries, PG and hyaluronan form a provisional matrix in response to local expression of growth factors such as TGF-beta-1 and platelet derived growth factor (15). The exact function of many PGs is unknown, but one of them, biglycan, has been implicated in collagen fibrillogenesis both in vitro (26) and in vivo (27), as well as in lipoprotein retention in atherosclerotic plaques (28).

More recently, studies of a rat model of infarct-induced CHF have demonstrated that biglycan is the primary PG expressed by cardiac fibroblasts in noninfarcted myocardium. The increased biglycan expression could be blocked either by an anti-TGF-beta-1 antibody or by the AT1R antagonist losartan, indicating that TGF-beta-1 released in response to AT1R stimulation was responsible for the increased biglycan expression (29,30).

Basic science implications. The primary result of the novel findings of Grande-Allen et al. (11) should be to stimulate more detailed studies regarding the specific types of cells and the specific ECM molecules that are present in CHF valves. For example, is the increased deoxyribonucleic acid content due to fibroblast proliferation, or are inflammatory cells also present? It is likely that the fibroblasts present in the CHF valves have an altered phenotype, with greater expression of AT1R and ECM. In addition, which specific GAG-containing matrix molecules are increased in amount in CHF valves? One obvious candidate is biglycan (29,30). Moreover, how does CHF alter valvular content and activity of matrix-degrading enzymes, such as matrix metalloproteinases, as well as of tissue inhibitors of metalloproteinases?

Also, as the authors suggest, animal models may be helpful in sorting out the relative effects of hemodynamic factors as opposed to cytokines and growth factors in the pathogenesis of mitral valve abnormalities. However, it would be important to analyze not only the measures of valve composition and regurgitation severity (12,13), but also the neurohormonal activation, as suggested by more recent studies of infarct-induced CHF (29,30). In addition, it may also be helpful to include comparative analyses of aortic valves in animal models of surgically induced CHF, as mitral valves would be subjected to relatively greater hemo-

dynamic force changes but both mitral and aortic valves would be subjected to neurohormonal activation. If the effect of CHF on aortic valves is studied in humans, it will be important to exclude valves with aortic sclerosis, as both proteoglycan content and fibroblast AT1R expression are altered in that condition (31). Moreover, based on the findings of Grande-Allen et al. (11), future investigations would also be well advised to heed the authors' warning that careful consideration should be given before including valves from explanted, end-stage cardiomyopathy hearts as "normal" controls.

Clinical implications. The clinical implications of the study are less clear, as it is not yet known to what extent mitral valve composition changes might contribute to MR severity in CHF patients. It is likely that changes in LV and mitral annular size and geometry due to pathologic remodeling, loading conditions, the severity of ventricular dyssynchrony, and abnormalities in regional wall motion and papillary muscle function are the major determinants of MR severity in CHF. In addition, it is likely that the neurohormonal alterations responsible for pathologic myocardial and annular remodeling in CHF also play an important role in mediating mitral valve compositional changes. In this regard, it would be helpful to include measures of neurohormonal markers, in addition to echocardiographic studies, in subsequent studies of CHF mitral valve composition. Moreover, pharmacologic therapies targeting neurohormonal activation, which are known to improve myocardial cellular and ECM composition, may also effect favorable changes in mitral valve composition in CHF. Regardless, the study of Grande-Allen et al. (11) should lead to a paradigm shift in our view of mitral valvular structure and composition in patients with CHF.

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